

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 29725P WO	FOR FURTHER ACTION	
International application No. PCT/EP2004/003238	International filing date (day/month/year) 26/03/2004	(Earliest) Priority Date (day/month/year) 28/03/2003

Applicant

BIOPHARM GESELLSCHAFT ZUR BIOTECHNOLOGISCHEN...

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 4 sheets.

It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

a. With regard to the language, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

The international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. With regard to any nucleotide and/or amino acid sequence disclosed in the International application, see Box No. I.

2. Certain claims were found unsearchable (See Box II).

3. Unity of invention is lacking (see Box III).

4. With regard to the title,

the text is approved as submitted by the applicant.

the text has been established by this Authority to read as follows:

5. With regard to the abstract,

the text is approved as submitted by the applicant.

the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. With regards to the drawings,

a. the figure of the drawings to be published with the abstract is Figure No. 1

as suggested by the applicant.

as selected by this Authority, because the applicant failed to suggest a figure.

as selected by this Authority, because this figure better characterizes the invention.

b. none of the figures is to be published with the abstract.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/EP2004/003238

Box No. IV Text of the abstract (Continuation of item 5 of the first sheet)

The present invention relates to an osteoinductive material comprising a matrix material with morphogenetic protein(s) absorbed on inner or outer surfaces of this matrix material, wherin the osteoinductive material is obtainable by contacting the matrix material and the morphogenic protein(s) under condtions of pH and ionic concentration to keep protein stable and dissolved in a solution until dried and thereby allowing that the matrix material becomes evenly coated with the morphogenic protein(s)

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International application No.
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Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: — because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 26-29 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

 International Application No
 PCT/EP2004/003238

 A. CLASSIFICATION OF SUBJECT MATTER
 IPC 7 A61L27/34 A61L27/56 C07K14/475

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
 IPC 7 A61L C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 6 118 043 A (DINGELDEIN ELVIRA ET AL) 12 September 2000 (2000-09-12) claims 1,7-13,19 -----	1-29
A	WO 94/15653 A (GENENTECH INC) 21 July 1994 (1994-07-21) claims 1-4,9,10,17 -----	1-29

 Further documents are listed in the continuation of box C. Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *&* document member of the same patent family

Date of the actual completion of the international search

22 September 2004

Date of mailing of the international search report

04/10/2004

 Name and mailing address of the ISA
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Authorized officer

Heck, G

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No	
PCT/EP2004/003238	

Patent document cited in search report	Publication date		Patent family member(s)		Publication date
US 6118043	A	12-09-2000	DE 4121043 A1 AT 176161 T AU 652839 B2 AU 1854692 A CA 2072244 A1 CZ 9201946 A3 DE 59209624 D1 EP 0520237 A2 ES 2128330 T3 HU 65499 A2 IE 922067 A1 JP 7171211 A JP 2003093495 A MX 9203253 A1 NO 922511 A PL 295001 A2 RU 2062622 C1 ZA 9204780 A		07-01-1993 15-02-1999 08-09-1994 07-01-1993 27-12-1992 13-01-1993 11-03-1999 30-12-1992 16-05-1999 28-06-1994 30-12-1992 11-07-1995 02-04-2003 31-03-1994 28-12-1992 28-12-1992 27-06-1996 28-04-1993
WO 9415653	A	21-07-1994	AT 153535 T AU 671721 B2 AU 6026294 A CA 2151486 A1 DE 69403439 D1 DE 69403439 T2 DK 679097 T3 EP 0679097 A1 ES 2105641 T3 GR 3024277 T3 JP 3347144 B2 JP 8505548 T WO 9415653 A1 US 5422340 A		15-06-1997 05-09-1996 15-08-1994 21-07-1994 03-07-1997 23-10-1997 22-12-1997 02-11-1995 16-10-1997 31-10-1997 20-11-2002 18-06-1996 21-07-1994 06-06-1995

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (PCT Rule 43bis.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION

See paragraph 2 below

International application No. PCT/EP2004/003238	International filing date (day/month/year) 26.03.2004	Priority date (day/month/year) 28.03.2003
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International Patent Classification (IPC) or both national classification and IPC
A61L27/34, A61L27/56, C07K14/475

Applicant
BIOPHARM GESELLSCHAFT ZUR BIOTECHNOLOGISCHEN...

1. This opinion contains indications relating to the following items:

- Box No. I Basis of the opinion
- Box No. II Priority
- Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- Box No. IV Lack of unity of invention
- Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- Box No. VI Certain documents cited
- Box No. VII Certain defects in the international application
- Box No. VIII Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:



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WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**Box No. I Basis of the opinion**

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
 - This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).
2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
 - a. type of material:
 - a sequence listing
 - table(s) related to the sequence listing
 - b. format of material:
 - in written format
 - in computer readable form
 - c. time of filing/furnishing:
 - contained in the international application as filed.
 - filed together with the international application in computer readable form.
 - furnished subsequently to this Authority for the purposes of search.
3. In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

Box No. II Priority

1. The following document has not been furnished:

- copy of the earlier application whose priority has been claimed (Rule 43bis.1 and 66.7(a)).
- translation of the earlier application whose priority has been claimed (Rule 43bis.1 and 66.7(b)).

Consequently it has not been possible to consider the validity of the priority claim. This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.

2. This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43bis.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

the entire international application,
 claims Nos. 26-29

because:

the said international application, or the said claims Nos. 26-29 relate to the following subject matter which does not require an international preliminary examination (specify):

see separate sheet

the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (specify):
 the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
 no international search report has been established for the whole application or for said claims Nos.
 the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form

has not been furnished

does not comply with the standard

the computer readable form

has not been furnished

does not comply with the standard

the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-bis of the Administrative Instructions.

See separate sheet for further details

**Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or
industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Yes: Claims	1-25
	No: Claims	-
Inventive step (IS)	Yes: Claims	-
	No: Claims	1-25
Industrial applicability (IA)	Yes: Claims	1-25
	No: Claims	-

2. Citations and explanations

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Since claims 26-29 are directed to a method of treatment of the human or animal body by surgery/therapy, they relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. For the assessment of the subject-matter of present claims 26-29 on the question whether it is industrially applicable, no unified criteria exist in the PCT Contracting States.

Therefore, no opinion will be formulated with respect to the subject-matter of claims 26-29 (Article 34(4)(a)(i) PCT).

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

The following document (D1) cited in the International search report is referred to in this communication; the numbering will be adhered to in the rest of the procedure:

D1: US 6,118,043 A (Nies B. et al.)

Novelty

Document D1 discloses (cf. claims 1, 7-13, 19) a bone replacement material comprising a porous matrix and fibroblast growth factor (FGF) adsorbed thereon. The material is prepared by impregnating the porous matrix with a solution of FGF followed by drying. The subject-matter of claims 1-25 of the present application differs from the disclosure of D1 by the choice of pH and ionic concentration of the morphogenetic protein solution and is therefore novel according to Article 33(2) PCT.

Inventive Step

Document D1, which is considered to represent the most relevant prior art, discloses (claims 1, 7-13, 19) the impregnation of porous implants with a solution of 50 µg FGF to provide a bone replacement material having a biological activity as close as possible to that of endogenous bone transplantation.

In view of D1, the objective technical problem underlying the present application can be formulated as to provide osteoinductive matrix materials for use in the pharmaceutical field which are homogeneously coated with morphogenetic proteins.

The solution proposed in the present application is a porous osteoinductive material comprising a matrix material having morphogenetic protein(s) adsorbed on inner or outer surfaces thereon, which can be obtained by selecting a pH and an ionic concentration of the solution that avoid precipitation of the morphogenetic proteins.

The expression "contacting the matrix material and the morphogenetic protein(s) under suitable conditions to keep the protein stable and dissolved in a solution until dried" in claim 1 refers to a desirable result without indicating the technical features necessary to obtain it. This leads to a lack of clarity of the claim (Article 6 PCT). The technical contribution of the present invention is not the theoretical finding that a complete dissolution of the morphogenetic protein allows a more homogeneous coating of the matrix material, but the realisation how to enhance both protein stability and solubility during the coating process, which is attainable by selection and control of the pH and low ionic concentrations using suitable buffers/solvents or specific additives (cf. description, p. 7, l. 28-31 and p. 9, l. 4-14). These features should be included in claim 1 to make the claim clear.

Due to the lack of the above-mentioned essential features in claim 1, the subject-matter of claims 1-25 is at present not considered to involve an inventive step according to Article 33(3) PCT. Should the Applicant, however, include those features into claim 1, the following statement would apply:

Since the relation between the pH and low ionic concentration of the morphogenetic protein solution on the one hand and the solubility of the morphogenetic proteins on the other hand is unexpected and allows to obtain a more homogeneous coating of the matrix material, the subject-matter of claims 1-25 is based on an inventive activity according to Article 33(3) PCT.